The clinical significance of whole blood viscosity in (cardio)vascular medicine

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Whole blood is a non-Newtonian fluid, which means that its viscosity depends on shear rate. At low shear, blood cells aggregate, which induces a sharp increase in viscosity, whereas at higher shear blood cells disaggregate, deform and align in the direction of flow. Other important determinants of blood viscosity are the haematocrit, the presence of macromolecules in the medium, temperature and, especially at high shear, the deformability of red blood cells. At the sites of severe atherosclerotic obstructions or at vasospastic locations, when change of vessel diameter is limited, blood viscosity contributes to stenotic resistance thereby jeopardising tissue perfusion. However, blood viscosity plays its most important role in the microcirculation where it contributes significantly to peripheral resistance and may cause sludging in the postcapillary venules. Apart from the direct haemodynamic significance, an increase in blood viscosity at low shear by red blood cell aggregation is also associated with increased thrombotic risk, as has been demonstrated in atrial fibrillation. Furthermore, as increased red blood cell aggregation is a reflection of inflammation, hyperviscosity has been shown to be a marker of inflammatory activity. Thus, because of its potential role in haemodynamics, thrombosis and inflammation, determination of whole blood viscosity could provide useful information for diagnostics and therapy of (cardio)vascular disease. (*Neth Heart J* 2002;10:512-6.)

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The viscosity of blood is its intrinsic resistance to flow, which arises from frictional interactions between all major blood constituents, i.e. plasma, plasma proteins and red blood cells, when blood flows through vessels. Because red blood cells (RBCs) are the main constituent of the cellular phase of blood, white blood cells and platelets normally do not have a great influence on whole blood viscosity. When blood flows through a vessel, adjacent liquid layers move with different velocities (figure 1).[1,2] The physical measure 'shear rate' is defined as the ratio of the velocity difference between two points, divided by the distance between the points. As a result its dimension is (cm/s)/cm or simply s^{-1}. As the frictional force, expressed in N(ewton), is dependent on the area (A) of contacting fluid layers, normalisation of the force for the contact area results in 'shear stress' having the dimension N/m^2 or Pa. The frictional force (F) between adjacent layers is directly proportional to shear rate and to the internal frictional property of the fluid called viscosity. Therefore, viscosity is shear stress divided by shear rate and has the dimension Pa.s. It is important to know that at the wall, velocity is zero and as the distance from the wall increases, an increase in velocity will be observed reaching its maximum near the centre. On the other hand, shear rate in the centre of the wall is zero and is highest at the vessel wall.

Because of the blood's high cellular content and the shear rate dependent interaction between these components, whole blood viscosity is not constant but depends on shear rate.[3-5] This behaviour is called non-Newtonian, in contrast to simple Newtonian fluids

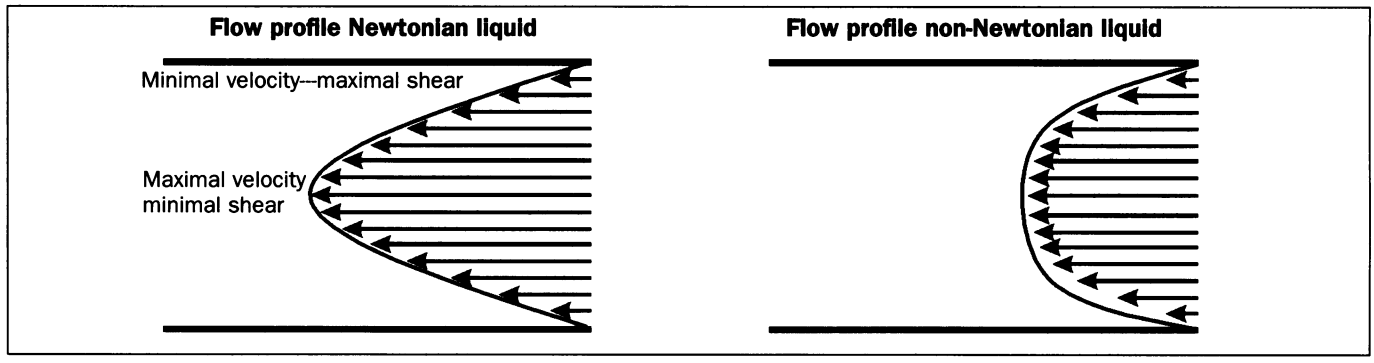

Figure 1. Schematic flow velocity model of Newtonian and non-Newtonian liquids with parabolic and flat ('plug-flow') profile, respectively; in the centre maximal velocity and minimal shear exist, whereas at the vessel wall minimal velocity and maximal shear. Viscosity=shear stress/shear rate.

like water. In low shear conditions the tendency of RBCs to aggregate becomes most prominent ('rouleaux formation'), which causes an exponential increase of viscosity with decreasing shear rate. At high shear rate the RBCs aggregating forces will be overruled by the shear stress acting between the fluid layers. Moreover, the individual red cells will deform and align in the direction of flow, thereby reducing the frictional forces caused by the red cells themselves and viscosity will reach a constant value in an asymptotic way and hence becomes almost Newtonian.

Because of this non-Newtonian character, blood tends to separate in two different phases near the vessel wall, where shear rate is highest. In direct contact with the wall a low viscosity phase exists, which is deficient in cells and rich in plasma and acts as a lubricant for the blood transport.[6] This effect explains the steep rise in velocity near the wall as depicted in figure 1. In contrast, in the middle of the vessel, where shear rate is low, RBC aggregation is predominant and therefore local viscosity rises, which reduces the differences in velocity in adjacent central fluid layers. Consequently, the blood flow velocity profile is rather flat in the middle (figure 1). Both effects lead to a so-called 'plug flow' velocity profile in the arteries, which deviates from a simple Newtonian parabolic velocity profile.

From this general description it will be clear that properties of the RBC, i.e. its aggregating tendency as well as its flexibility, are main determinants of blood viscosity and in this respect particularly their volume concentration, i.e. the haematocrit, is the most important parameter of blood viscosity. When RBCs are washed and suspended in physiological saline or when they are hardened, the non-Newtonian behaviour is substantially reduced, because rouleaux formation is diminished at low shear and RBC deformability is impaired at high shear.[6] Figure 2 depicts how whole blood viscosity, especially under low shear conditions, will drop when the haematocrit decreases or will rise when more plasma proteins stimulating red blood cell aggregation (especially fibrinogen or other 'acute phase' macromolecules) are present.[1,2]

Haemodynamic implications of blood viscosity

Blood viscosity has an important influence on tissue perfusion.[7,8] This is demonstrated in the Hagen-Poisseuille equation which describes the flow through a simple tube related to the tube's dimensions, the pressure drop over the tube and the viscosity of the Newtonian fluid passed: $Q = \Delta P\ \pi.r^4/8l\eta$, in which Q= total flow, ΔP= pressure gradient, r=vessel radius, l= tube length and η= blood viscosity. Because a rise of haematocrit increases viscosity, this may decrease tissue perfusion. Therefore, an optimal haematocrit for tissue oxygenation exists.[9] Furthermore, when blood viscosity rises because of high levels of aggregating proteins (fibrinogen, CRP or other 'acute-phase' proteins) the optimum haematocrit becomes lower. From the equation it becomes clear that vasodilating drugs have a great impact on peripheral resistance, because r shows up to the fourth power in this equation. However, in narrowed arteries or in severe vasospasm, in which dilating capacity is diminished, the contribution of blood viscosity to whole bed resistance and tissue perfusion becomes more important.[10,11] Several studies have also shown a linkage between whole blood viscosity and the haemodynamics of hypertension and that a significant correlation exists between whole blood viscosity and the presence of left ventricular hypertrophy.[12,13]

Blood viscosity and the microcirculation

Reaching the arterioles RBC aggregates disperse due to increased shear, after which RBCs flow as individual cells through the capillaries. After capillary passage they again form aggregates within the collecting venules. This implies that flow resistance in the capillary system is especially influenced by the deformability of the RBCs. Factors that increase aggregation, such as fibrinogen or other 'acute-phase' proteins, increase flow resistance in the post-capillary venules and cause 'sludging' of the blood.[7] In on-pump heart surgery, the

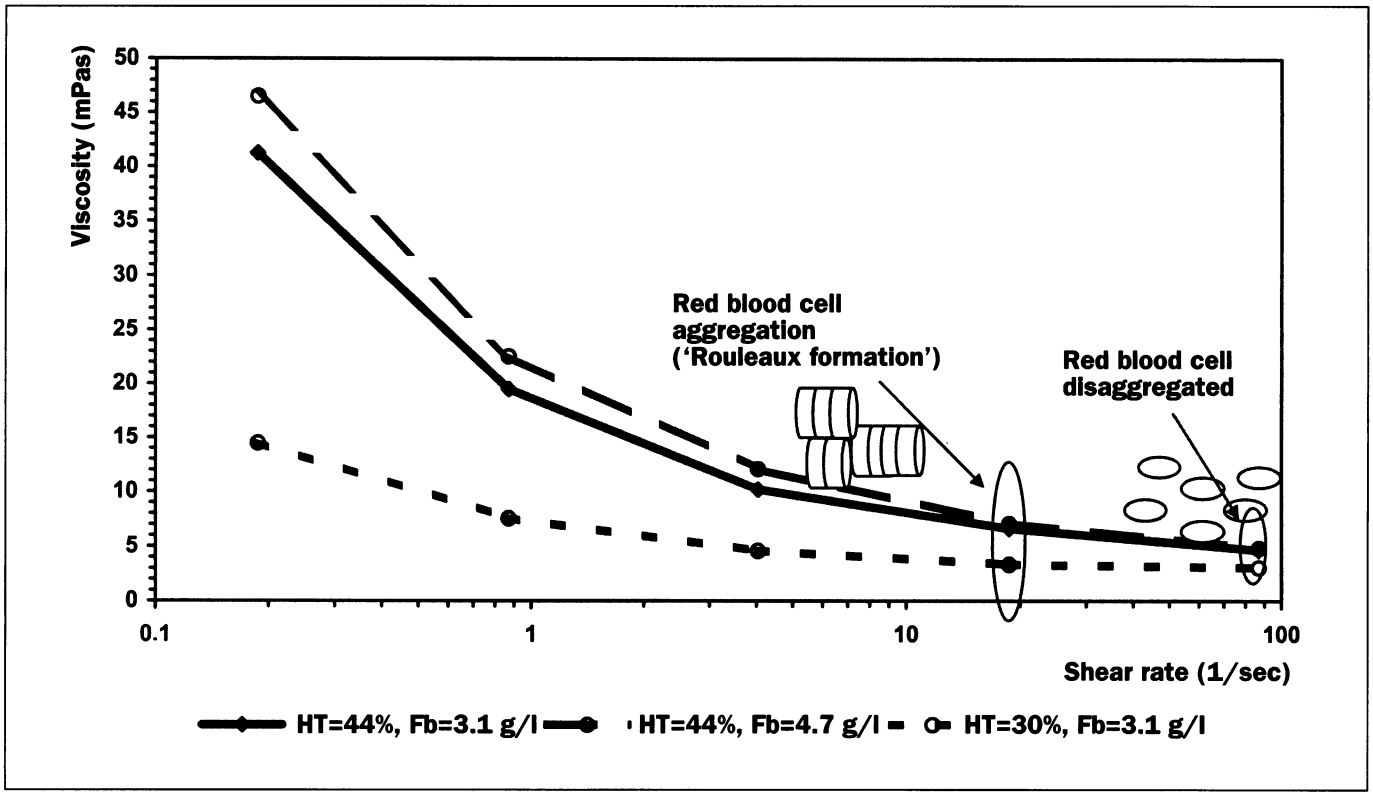

Figure 2. Diagram illustrating rheology of whole blood. From high to low shear rate RBC aggregation generally becomes of most interest at a shear rate of 25 sec^{-1}, when blood shows most of its non-Newtonian character. RBCs become completely disaggregated at a shear rate of 100 to 200 sec^{-1} and viscosity only slightly decreases further at higher shear rates (Newtonian). In the figure the influence of increased fibrinogen level and fall of haematocrit is also depicted.

extra-corporeal circulation and hypothermia affect the deformability of the RBCs[14] and an 'acute-phase' reaction is induced.[15] These factors might contribute to a diffuse cerebral microcirculatory disorder and could be one of the principal factors leading to neurocognitive dysfunction described after this type of surgery.[16] In all circumstances, because of its non-Newtonian character, a decrease in blood flow velocity in the microcirculation will contribute to an increase in blood viscosity. This accentuates a reduction in blood transport in case of a diminished driving pressure or when cells become less flexible. Although arteriovenous fistulas often exist in the microcirculatory bed to bypass the encountered resistance, tissue extraction of oxygen will nevertheless be impaired.[17]

Blood viscosity and thromboembolic risk

Sigel et al. demonstrated that aggregation of RBCs ('rouleaux formation') causes increased echogenicity.[18] Thus, appearance of spontaneous echo contrast in the left atrium (SCLA) in patients with atrial fibrillation is a sign of hyperviscosity through stagnant flow (figure 3). This is in concordance with the findings of Black et al., who showed that the presence of SCLA is not only a reflection of haemodynamic abnormalities such as stasis or enlarged left atrium, but also of haematological changes as increased haematocrit or fibrinogen.[19] Moreover, SCLA is strongly linked with thromboembolic risk.[20] It is important to note that administration of oral anticoagulants does not diminish the

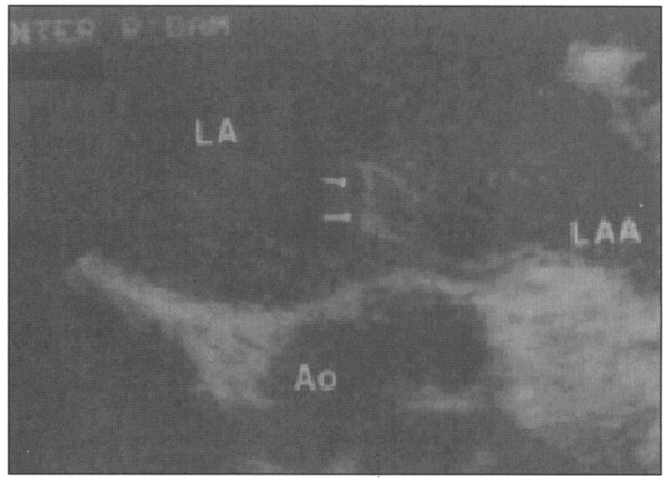

Figure 3. Transoesophageal echocardiography of the left atrium (LA), in which near the appendage (LAA) spontaneous echo contrast can be observed (arrows). Ao=aorta.

presence of SCLA, although they do diminish the thromboembolic risk.[21]

Blood viscosity and atherosclerosis

Atherosclerosis is now considered a chronic inflammatory disease[22,23] and the determination of 'acute-phase' proteins has improved short- and long-term cardiovascular risk assessment in individuals with known coronary disease[24] and in apparently healthy populations.[25] A common characteristic of most 'acute-phase' proteins is that they increase RBC aggregation[26] and hence RBC aggregation has been used for many years as a marker of systemic inflammation.[27,28] Because increased RBC aggregation raises whole blood viscosity, particularly at low shear rate, whole blood viscosity is generally found to be increased in patients with atherosclerosis.[29] Levels of whole blood and plasma viscosity predict future cardiovascular events, both short[30] and long term,[31] confirming the linkage between viscosity and the level of 'acute-phase' proteins. Blood viscosity itself has been proposed to play a pathophysiological role in atherogenesis,[2,32,33] although this subject is controversial and warrants further study.

Circadian rhythm of blood viscosity

An important aspect of blood viscosity is its circadian variation,[34] which correlates with the change in haematocrit during the day, but also with changes in plasma protein levels such as fibrinogen or interleukin-6.[35] Because blood viscosity rises exponentially at lower shear rate with higher haematocrit and increasing plasma protein levels, the percentage change of mean blood viscosity at lowest shear can vary between 62 and 136%.[34] The circadian rhythm may also explain the increased incidence of acute coronary syndromes and stroke in the morning hours.[36,37] It may also be the reason why the efficacy of thrombolytics varies during the day.[38]

Therapeutic implications of hyperviscosity

The therapeutic options for treating hyperviscosity in (cardio)vascular disease are manifold and can often be accomplished in an easy and cost-effective way. Haemodilution therapy has a tradition of many centuries, going back to the era of humoral medicine in which bloodletting was an obligatory remedy for a whole spectrum of diseases.

In the sixties, long before thrombolytics or angioplasty became available in cardiovascular disease, phlebotomy was advocated in patients with angina pectoris and myocardial infarction by some clinicians if the haematocrit on admission was higher than 50%.[39] Although phlebotomy in these patients has become obsolete, several studies have underscored the pathophysiological role of elevated haematocrit and viscosity during acute coronary syndromes.[40-42] In fact one of the additional benefits of the thrombolytic streptokinase has been attributed to its reduction of blood viscosity by lowering the fibrinogen level.[43] Animal experiments have shown that haemodilution reduces the occurrence of arterial thrombosis[44] and applied during acute myocardial infarction it reduces mean infarct size.[45] The hyperviscosity of blood induced by hypothermia during on-pump heart surgery is partially counteracted by considerable haemodilution perioperatively.[46]

The role of haemodilution in ischaemic stroke, which is a major cause of disability in the Western world, is still under debate. Although some clinical trials investigating haemodilution therapy did not show encouraging results,[47] basic research investigations[48-50] and other clinical trials, did show significant benefit when haemodilution was performed in a customised rather than in a standard manner[51] or when haemodilution was combined with venesection in the early phase.[52] Haemodilution to improve brain perfusion during cerebral vasospasm in subarachnoid haemorrhage is a well-established therapy.[10]

Conclusion

Blood viscosity plays an important role in the pathophysiology of vascular diseases as a determining factor of global cardiovascular load and as a factor affecting regional tissue perfusion. A high blood viscosity also increases thromboembolic risk and is correlated with the presence of systemic inflammation. Most important contributors to an increased viscosity are haematocrit, higher level of inflammatory proteins and loss of red cell flexibility. Applying rational strategies focusing on the characterisation and modification of blood viscosity has shown to improve diagnostics and therapy in vascular disorders. ■

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